

Best Available Copy

BW

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>5</sup> :  <b>A61K 31/55</b>	<b>A2</b>	(11) International Publication Number: <b>WO 93/00094</b>
		(43) International Publication Date: <b>7 January 1993 (07.01.93)</b>
<p>(21) International Application Number: <b>PCT/GB92/01083</b></p> <p>(22) International Filing Date: <b>17 June 1992 (17.06.92)</b></p> <p>(30) Priority data:              9113379.3                      21 June 1991 (21.06.91)      GB              9113377.7                      21 June 1991 (21.06.91)      GB</p> <p>(71) Applicant (for all designated States except US): <b>SMITH-KLINE BEECHAM PLC (GB/GB); New Horizons Court, Brentford, Middlesex TW8 9EP (GB).</b></p> <p>(72) Inventors; and          (75) Inventors/Applicants (for US only) : <b>WARD, John, Gérard [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). YOUNG, Rodney, Christopher [GB/GB]; SmithKline Beecham Pharmaceuticals, The Fryth, Welwyn, Hertfordshire AL 6 9AR (GB). KAUMANN, Alberto, Julio [AR/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).</b></p>	<p>(74) Agents: <b>FLORENCE, Julia, A. et al.; Corporate Patents, SmithKline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).</b></p> <p>(81) Designated States: <b>AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE).</b></p> <p><b>Published</b>  <i>Without international search report and to be republished upon receipt of that report.</i></p>	
<p>(54) Title: <b>MEDICAMENTS</b></p> <p>(57) Abstract</p> <p><b>Tetrahydrobenzazepine derivatives are disclosed as medicaments.</b></p>		

Best Available Copy

Best Available Copy

# FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	MI	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	GA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BF	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	RO	Romania
CA	Canada	IT	Italy	RU	Russian Federation
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark	MG	Madagascar		
ES	Spain				

## MEDICAMENTS

The present invention relates to certain tetrahydro-  
5 benzazepine derivatives for use in the treatment of disorders  
characterised by excessive vasodilatation, in particular the  
treatment of portal hypertension and the treatment and  
prophylaxis of migraine, and more generally to the use of  
5-HT<sub>2</sub> and 5-HT<sub>1</sub>-like receptor agonists in the treatment of  
10 portal hypertension and to the use of 5-HT<sub>2</sub> agonists in the  
treatment and prophylaxis of migraine.

Portal hypertension, which is commonly associated with  
cirrhosis of the liver is characterised by increased portal  
15 venous blood flow, (which is caused by dilatation of  
mesenteric arterioles), and increased portal vascular  
resistance. A serious complication of this condition is  
rupture of esophageal varices or paraesophageal collaterals,  
which develop to reduce portal pressure.

20

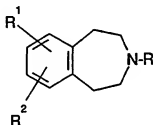
It has now been found that certain tetrahydro-  
benzazepines known in the art for the treatment of  
gastrointestinal motility disorders are agonists at 5-HT<sub>2</sub>  
and/or 5-HT<sub>1</sub>-like-receptors and are expected to have utility  
25 in the treatment of portal hypertension.

Migraine is a non-lethal disease suffered by one in ten  
individuals. The main symptom is headache; other symptoms  
include vomiting and photophobia. Currently, the most  
30 widely used treatment for migraine involves administration of  
ergotamine, dihydroergotamine or methysergide. All these  
drugs are inter alia agonists of 5HT<sub>1</sub>-like receptors but also  
have other actions; treatment with them is associated with a  
number of adverse side effects. In addition, some patients  
35 experience a "withdrawal headache" following the cessation of  
treatment with an ergot product, such as ergotamine, causing  
them to repeat the treatment and resulting in a form of  
addiction.

In view of the foregoing, there is clearly a need for the provision of effective and safe medicaments for the treatment of migraine.

- 5 It has now been found that certain tetrahydro-benzazepines known in the art for the treatment of gastrointestinal motility disorders are agonists at 5HT<sub>1</sub>-like and/or 5HT<sub>2</sub>-receptors and are expected to have utility in the treatment of migraine.

10 The present invention therefore provides compounds of structure (I):



Structure (I)

15

in which:

- R is hydrogen, C<sub>1</sub>-6alkyl or C<sub>3</sub>-5alkenyl;  
R<sup>1</sup> is NO<sub>2</sub>, cyano, halo, COR<sup>3</sup>, SO<sub>n</sub>R<sup>4</sup> or SO<sub>n</sub>NR<sup>5</sup>R<sup>6</sup>;  
20 R<sup>2</sup> is hydrogen, hydroxy or C<sub>1</sub>-4alkoxy;  
R<sup>3</sup> is hydrogen, C<sub>1</sub>-4alkyl, OR<sup>5</sup> or NR<sup>5</sup>R<sup>6</sup>;  
R<sup>4</sup> is C<sub>1</sub>-6alkyl or halo C<sub>1</sub>-6 alkyl;  
R<sup>5</sup> and R<sup>6</sup> are hydrogen, C<sub>1</sub>-6alkyl or C<sub>3</sub>-6 cycloalkyl; and n is 1 or 2;  
25 and pharmaceutically acceptable salts thereof for use in the manufacture of a medicament for the treatment of portal hypertension and/or migraine.

- 30 Suitably R is hydrogen, C<sub>1</sub>-6alkyl or C<sub>3</sub>-5alkenyl;  
preferably R is hydrogen.

Suitably  $R^1$  is nitro, cyano, halo,  $COR^3$ ,  $SO_nR^4$  or  $SO_nNR^5R^6$ ; preferably  $R^1$  is  $SO_nR^4$ , nitro or halo; most preferably  $R^1$  is  $SO_nR^4$ .

5           Suitably  $n$  is 1 or 2; preferably  $n$  is 2.

Suitably  $R^2$  is hydrogen, hydroxy or  $C_{1-4}$ alkoxy; preferably  $R^2$  is  $C_{1-4}$ alkoxy or hydroxy.

10           Suitably  $R^3$  is hydrogen,  $C_{1-4}$ alkyl,  $OR^5$  or  $NR^5R^6$ ; preferably  $R^3$  is  $C_{1-4}$ alkyl, in particular methyl.

Preferably the group  $R^1$  is at the 8-position and the group  $R^2$  is at the 7-position of the ring of the compound of structure (I).

15

Suitably  $R^4$  is  $C_{1-6}$ alkyl or halo  $C_{1-6}$  alkyl; preferably  $R^4$  is  $C_{1-6}$ alkyl, or  $C_{1-6}$  alkyl substituted by 1 to 6 halogen atoms (eg.  $CF_3$ ). and most preferably  $R^4$  is methyl.

20           Suitably  $R^5$  and  $R^6$  are hydrogen or  $C_{1-6}$ alkyl, or  $C_{3-6}$  cycloalkyl. Preferably, when both groups represent  $C_{1-6}$  alkyl, they are the same.

25            $C_{1-6}$ alkyl groups, either alone or as part of another group, can be straight or branched.

Suitable salts will be apparent to those skilled in the art, and include, for example, acid addition salts such as the hydrochloride, or the oxalate.

30

Suitable examples of compounds for use in the present invention are as described in EP-0229510-B, for example :

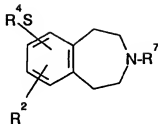
35   7-hydroxy-8-sulphamoyl-2,3,4,5-tetrahydro-1H-benzazepine, and 7-hydroxy-8- (N,N-dimethylsulphamoyl)-2,3,4,5-tetrahydro-1H-benzazepine.

- In particular the present invention relates to the use of a compound in which R is hydrogen, R<sup>1</sup> is methylsulphonyl and R<sup>2</sup> is hydroxy, namely, 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of migraine.

- Certain compounds falling within the scope of structure (I) are themselves novel and as such form a further aspect of the invention. These compounds are in particular:
- 7-methoxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine oxalate;
  - 7-methoxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride;
  - 7-hydroxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride;
  - 7-methoxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride;
  - 7-hydroxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride;
  - 7-methoxy-6-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride;
  - 6-bromo-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride;
  - 8-acetyl-7-hydroxy-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride;
  - 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine; and
  - 7-hydroxy-8-trifluoromethylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine.

Compounds of structure (I) may be prepared by the methods described in EP 0229510-B, or by the following methods :

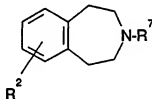
- a) to prepare a compound of structure (I) where R<sup>1</sup> represents -SO<sub>n</sub>R<sup>4</sup>, the reaction of a compound of structure (II) :



Structure (II)

(wherein  $R^2$  and  $R^4$  are as hereinbefore defined and  $R^7$  is an  
 5 N-protecting group) with an oxidising agent, in the presence  
 of titanium trichloride;

b) to prepare a compound of structure (I) wherein  $R^1$   
 represents  $-COR^3$ ,  $NO_2$  or halogen, the reaction of a compound  
 10 of structure (III) :



Structure (III)

15 (wherein  $R^2$ ,  $R^3$  and  $R^7$  are as hereinbefore defined) with an  
 appropriate acylating, nitrating or halogenating agent  
 respectively; followed in each case by removal of the N-  
 protecting group, and if desired salt formation.

20 Suitable N-protecting groups  $R^7$  are well known in the  
 art and include acyl groups such as acetyl, trifluoroacetyl,  
 benzoyl, methoxycarbonyl, and benzyloxycarbonyl. N-  
 deprotection may be carried out by conventional methods.

25 In process (a) the oxidising agent may be for example  
 hydrogen peroxide or a peracid such as 3-chloroperbenzoic  
 acid, in a solvent such as acetic acid. It will be

appreciated that one equivalent of the oxidising agent will produce a compound wherein n is 1 and two or more equivalents will give a compound wherein n is 2.

5 In process (b) the acylating agent may be for example an acid chloride or acid anhydride corresponding to the group  $R^3CO-$ . The reaction is desirably effected in the presence of tin tetrachloride. Nitration may be effected using concentrated nitric acid in admixture with acetic anhydride, followed by neutralisation with e.g. sodium bicarbonate, 10 Halogenation may be carried out with an acidic solution of a halogen e.g.  $Br_2$  in acetic acid, followed by neutralisation with e.g. sodium bicarbonate. In general the nitration and halogenation reactions will result in a mixture of isomeric 15 compounds, substituted respectively at the 7,8' and 6,7 positions of the benzazepine ring, which may be separated for example by chromatography, or crystallisation.

The compounds of structure (I) have been found to be 20 agonists at 5-HT<sub>2</sub> and/or 5-HT<sub>1</sub>-like receptors and are expected to have utility in medicine in the treatment or prophylaxis of portal hypertension. Whilst not wishing to be bound by theory, it is believed that 5-HT<sub>1</sub>-like agonists and 5-HT<sub>2</sub>-agonists are effective in portal hypertension 25 through constriction of mesenteric arterioles, and partial constriction of paraesophageal collaterals with consequent reduction of portal flow and portal pressure. Preferred compounds for use according to the present invention are partial agonists at 5-HT<sub>2</sub> receptors and/or 5-HT<sub>1</sub>-like 30 receptors.

It is believed that the use of 5-HT<sub>2</sub> and 5-HT<sub>1</sub>-like-receptor agonists in the treatment of portal hypertension has not previously been described and hence represents a novel 35 use for these classes of compounds. In a further aspect therefore the present invention provides 5-HT<sub>2</sub> receptor agonists and 5-HT<sub>1</sub>-like-agonists for use in the treatment of portal hypertension. The invention also provides the use of 5-HT<sub>2</sub> receptor agonists and 5-HT<sub>1</sub>-like-agonists in the 40 manufacture of a medicament for the treatment of portal



hypertension. Also provided is a method of treating portal hypertension which comprises administering to a subject in need thereof an effective amount of a 5-HT<sub>2</sub>-agonist or 5-HT<sub>1</sub>-like-agonist. For use according to the present invention a  
5 5-HT<sub>2</sub>-agonist or 5-HT<sub>1</sub>-like-agonist is preferably a partial agonist at the said receptor. Most preferably, a compound for use according to this invention is a partial agonist at both 5-HT<sub>2</sub> and 5-HT<sub>1</sub>-like receptors.

10 The compounds of structure (I) have been found to be agonists at 5HT<sub>1</sub>-like and/or 5HT<sub>2</sub> receptors and are expected to have utility in medicine in the treatment or prophylaxis of migraine. Whilst not wishing to be bound by theory, it  
15 is believed that 5HT<sub>1</sub>-like agonists are effective in migraine through constriction of cerebral arteries and that 5HT<sub>2</sub> agonists constrict the superficial temporal artery. Preferred compounds for use according to the present invention are partial agonists at 5HT<sub>1</sub>-like and/or 5HT<sub>2</sub> receptors.

20 It is believed that the use of 5-HT<sub>2</sub>-receptor agonists in the treatment of migraine has not previously been described and hence represents a novel use for this class of compound. In a further aspect therefore the present  
25 invention provides 5-HT<sub>2</sub>-receptor agonists for use in the treatment of migraine. The invention also provides the use of 5-HT<sub>2</sub>-receptor agonists in the manufacture of a medicament for the treatment of migraine. Also provided is a method of treating migraine which comprises administering to a subject  
30 in need thereof an effective amount of a 5-HT<sub>2</sub> agonist. For use according to the present invention a 5-HT<sub>2</sub>-agonist is preferably a partial agonist at this receptor.

35 In therapeutic use the compounds are incorporated into standard pharmaceutical compositions. They can be administered orally, parenterally, rectally or transdermally.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given

orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

5 A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

10 A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and  
15 cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared  
20 using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin  
25 capsule.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when administered parenterally (i.e. by injection or infusion)  
30 can be formulated as solutions or suspensions.

A composition for parenteral administration will generally consist of a solution or suspension of the active ingredient in a sterile aqueous carrier or parenterally  
35 acceptable oil, for example polyethyleneglycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository composition comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins  
5 or cocoa butter or other low melting vegetable or synthetic waxes or fats.

A typical transdermal formulation comprises a conventional aqueous or non-aqueous vehicle, for example,  
10 a cream, ointment lotion or paste or in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dose form. Each dosage unit for oral administration contains preferably from  
15 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 150 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 1000 mg, preferably between 1 mg and 400 mg, for example between 10 and 400 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg  
25 and 30 mg, for example between 1 and 30 mg of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy.

## BIOLOGICAL DATA

5-HT<sub>1</sub>-like Receptor Screen

## 5 Dog Saphenous Vein

Helicoids of dog saphenous vein were set up at 37°C in modified Krebs solution at a resting force of 10 mN. The solution also contained 1 µmol/l each of ketanserin prazosin, atropine and mepyramine, 6 µmol/l cocaine and 200 µmol/l ascorbate. Nearly isomeric contractions were measured with force transducers on a polygraph. The tissues were exposed twice to 5-hydroxytryptamine (5-HT) 2 µmol/l followed by washes. A cumulative concentration-effect curve to the test compound was determined, followed by a curve to 5-HT in the presence of the highest used concentration of test compound. Contractions caused by the test compound were compared with those caused by 5-HT. The intrinsic activity of the test compound was calculated as the ratio of the maximum test compound-induced effect over the effect caused by 2 µmol/l 5-HT. The EC<sub>50</sub> of the test compound was estimated from the corresponding effect curve. When appropriate equilibrium dissociation constraints K<sub>p</sub> were estimated by the method of Marano & Kaumann (1976, J. Pharmacol. Exp. Ther. 192, 518-525).

The compounds of structure (I) have been found to demonstrate activity in this screen, for example: 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine (prepared according to the procedures described in EP 229510-B), was found to have an EC<sub>50</sub> of 0.2 µM, and the compound of Example 1 an EC<sub>50</sub> of 20 µM.

## RABBIT BASILAR ARTERY

35

## METHODS

Experiments were performed in intracranial arteries from rabbit isolated basilar artery in a similar method to

one described previously (Parsons and Whalley, 1989. Eur J Pharmacol 174, 189-196.).

In brief, rabbits were killed by overdose with anaesthetic (sodium pentobarbitone). The whole brain was quickly removed and immersed in ice cold modified Krebs's solution and the basilar artery removed with the aid of a dissecting microscope. The Krebs solution was of the following composition (mM)  $\text{Na}^+$  (120);  $\text{K}^+$  (5);  $\text{Ca}^{2+}$  (2.25);  $\text{Mg}^{2+}$  (0.5);  $\text{Cl}^-$  (98.5);  $\text{SO}_4^{2-}$  (1); EDTA (0.04), equilibrated with 95%  $\text{O}_2$ /5%  $\text{CO}_2$ . The endothelium was removed by a gentle rubbing of the lumen with a fine metal wire. Arteries were then cut into ring segments (ca 4-5 mm wide) and set up for recording of isometric tension in 50 ml tissue baths in modified Krebs solution with the additional supplement of (mM);  $\text{Na}^{2+}$  (20); fumarate (10); pyruvate (5); L-glutamate (5) and glucose (10). The arteries were then placed under a resting force of 3-4 mN maintained at 37°C and the solution bubbled with 95%  $\text{O}_2$ /5%  $\text{CO}_2$ .

20

After tests for initial reactivity with 90 mM KCl depolarising solution and for lack of acetylcholine-induced relaxation of 5-HT (10 mM) precontraction, cumulative concentration-effect curves (2 nM-60 mM) to 5-HT were constructed in the presence of ascorbate 200 mM, cocaine 6 mM, indomethacin 2.8 mM, ketanserin 1 mM and prazosin 1 mM.

25

Following a 45-60 min wash period, cumulative concentration-effect curves to the test compounds or 5-HT (as a time match control) were constructed in the presence of ascorbate, indomethacin, cocaine, ketanserin and prazosin.

30

#### 5-HT<sub>2</sub>-Receptor Screen

Rat Tail Artery (Kaumann A.J. & Frenken M. 1988, J. Pharmacol. Exp. Pharmacol. 245, 1010-1015)

35

The ventral caudal artery was used from rats pretreated with reserpine 7mg/kg ip (20 h). Five interconnected arterial rings were prepared and set up to contract in

40

- 12 -

modified Krebs solution at 32.5°C as follows. Resting force of the rings was set to be 4 mN and the rings allowed to relax thereafter without further readjustment. Three cumulative concentration-effect curves were determined, the first to 5-HT followed by washout, the second to the test compound and the third to 5-HT in the presence of the highest used concentration of test compound. The intrinsic activity of the test compound was calculated as the ratio of the maximum test compound-induced effect over maximum 5-HT-induced effect. The EC<sub>50</sub> of the test compound was estimated from the corresponding concentration-effect curve. Equilibrium dissociation constants K<sub>p</sub> were estimated by the method of Marano & Kaumann (1976, J. Pharmacol. Exp. Ther., 198, 518-525).

15

The compounds of structure (I) have been found to demonstrate activity in this screen, for example, 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine was found to have an EC<sub>50</sub> of 2 µM, and the compound of Example 2 an EC<sub>50</sub> of 1 µM.

20

#### Portal Hypertension - In vivo

The effect of 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine was investigated on superior mesenteric arterial flow in conscious normal and portal vein-ligated rats (Sprague-Dawley). Portal hypertension in portal vein-ligated rats was produced as described (Groszmann et al. 1982). A Doppler flowmeter probe was implanted into the superior mesenteric artery for chronic studies. Superior mesenteric flow changes were observed during 4 days, followed by 4 days' exposure to 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine in the drinking water and another period of 4 days without 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine in the drinking water. 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine significantly reduced superior mesenteric flow in both sham-operated and portal vein-ligated rats. The effect was reversible during the last 4 day period without 7-hydroxy-8-

25

30

35

methysulphonyl-2,3,4,5-tetrahydro-1H-benzazepine in the drinking water.

- 5 Groszmann R J, Vorobioff J and Riley E (1982). Splachnic hemodynamics in portal hypertensive rats: measurement with gamma-labelled microspheres. Am J Physiol 242: G156-G160.

## PHARMACEUTICAL FORMULATIONS

## 1. Formulation for intravenous infusion

Compound of structure (I)	0.1 - 150 mg
Sodium hydroxide/hydrochloric acid	to pH ca 7
polyethylene glycol	0 - 30 ml
propylene glycol	0 - 30 ml
alcohol	0 - 10 ml
water	to 100 ml

## 2. Formulation for bolus injection

Compound of structure (I)	0.1 - 150 mg
sodium hydroxide or hydrochloric acid	to pH ca 7
polyethylene glycol	0 - 2.5 ml
alcohol	0 - 2.5 ml
water	to 5 ml

A toxicity adjusting agent eg. sodium chloride, dextrose or mannitol may also be added.

## 3. Tablet for oral administration

	mg/tablet
Compound of structure (I)	50
lactose	153
starch	33
crospovidone	12
microcrystalline cellulose	30
magnesium stearate	<u>2</u>
	280



### Examples

- Compounds within the scope of the present invention (e.g. 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-3-benzazepine) can be prepared using the methods described in EP-229510-B or the methods disclosed hereinbefore.

#### Example 1

- 10 **7-Methoxy-8-methylsulphinyl-,3,4,5-tetrahydro-1H-benzazepine monooxalate**

- 3-Acetyl-7-methoxy-8-methylthio-2,3,4,5-tetrahydro-1H-benzazepine (3.04g) was dissolved in methanol (500 ml) and treated with a 15% solution of titanium trichloride (11.8g), followed by 6% hydrogen peroxide solution (18.0g), dropwise, with stirring, over 10 minutes at room temperature. After stirring for a further 30 minutes, the reaction mixture was filtered, diluted with water and extracted with chloroform. The latter extract was washed with aqueous sodium sulphite, then water, dried, filtered, and evaporated to dryness leaving 3-acetyl-7-methoxy-8-methylsulphinyl-,3,4,5-tetrahydro-1H-benzazepine (3.21g) as a solid, m.p. 130-2°C.

- 25 The above product (20mg) was hydrolyzed by refluxing a solution in isopropanol (1ml) with 40% aqueous sodium hydroxide (1ml) for 60 hours. Most of the isopropanol was evaporated in vacuo, and the remaining solution was diluted with water, and extracted with chloroform. The extracts were combined, dried (MgSO<sub>4</sub>) and evaporated to give 7-methoxy-8-methylsulphinyl-,3,4,5-tetrahydro-1H-benzazepine (17mg) which was converted to the monooxalate salt, m.p. 212-4°C.

## Example 2

## 7-Methoxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride

5 Concentrated nitric acid (0.6ml, 70% w/w) was added to a stirred, ice-cooled solution of 3-acetyl-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine (1.98g) in acetic anhydride (30ml) over 5-6 hours. The solution was allowed to warm to  
10 room temperature and, after standing overnight, was added to saturated aqueous sodium bicarbonate. When all of the excess acetic anhydride had reacted, the resulting mixture was saturated with sodium chloride and extracted with ethyl acetate. The combined extracts were washed with water,  
15 dried (MgSO<sub>4</sub>) and evaporated to a gum, which was purified by chromatography (SiO<sub>2</sub>; C<sub>6</sub>H<sub>14</sub>/EtOAc) to give 3-acetyl-7-methoxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine (0.93g), m.p. 127-132°C, and 3-acetyl-6-nitro-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine which was recrystallised from  
20 benzene (0.16g), m.p. 143-149°C.

The above product (3-acetyl-7-methoxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine) (0.90g) was heated at reflux in 3N.HCl (54ml) for 16 hours. The resulting  
25 solution was evaporated to dryness to leave a yellow solid which was triturated with acetone and collected by filtration. The beige solid thus obtained was dried over P<sub>2</sub>O<sub>5</sub> and recrystallised from methanol to give 7-methoxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride  
30 (0.74g), m.p. 234-7°C.

## Example 3

## 7-Hydroxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride

35 7-Methoxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride (0.40g) was dissolved in 48% aqueous hydrobromic acid, and the solution was heated to reflux for  
40 24 hours. The solution was evaporated to dryness to leave a

crude yellow solid which was basified and purified by chromatography ( $\text{SiO}_2$ ;  $\text{CHCl}_3/\text{MeOH}$ ), then recrystallised from methanol/conc. hydrochloric acid to give 7-hydroxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride (0.11g), m.p. 251-5°C.

#### Example 4

##### 7-Methoxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride

3-Acetyl-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine (5.0g) was dissolved in glacial acetic acid (70ml) and heated to 70°C. A 1.0M solution of bromine in acetic acid was added over 20-30 minutes, and the resulting solution was heated at 70°C for a further hour. The solution was allowed to cool overnight, during which a mass of beige crystals was obtained. These were collected by filtration, basified and purified by chromatography ( $\text{SiO}_2$ ;  $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ ), followed by crystallisation from ethyl acetate/ether to give 3-acetyl-7-methoxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine (1.55g), m.p. 123-125°C, and 3-acetyl-6-bromo-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine, m.p. 99-101°C.

The above product (3-acetyl-7-methoxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine) (0.30g) was heated under reflux in 3M HCl (16.5ml) for 20 hours. The solution was evaporated to dryness in vacuo and triturated with acetone to give 7-bromo-8-methoxy-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride as a white solid (0.25g), m.p. 268-272°C.

#### Example 5

##### 7-Hydroxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride

A solution of 3-acetyl-7-methoxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine (0.5 g) in dichloromethane (12 ml) was cooled in an acetone/dry ice bath. Boron tribromide

(0.32 ml) was added to the stirred solution in one portion, and the mixture was allowed to warm to room temperature over 1 hour. Stirring was continued for a further 30 minutes, then water was added. The mixture was partitioned between  
5 water and dichloromethane, and the aqueous layer was re-extracted with dichloro-methane. The combined extracts were washed with water and brine, dried ( $\text{MgSO}_4$ ) and evaporated to a solid, which was purified by chromatography ( $\text{SiO}_2$ ;  $\text{CHCl}_3/\text{MeOH}$ ) to give 3-acetyl-7-hydroxy-8-bromo -2,3,4,5-  
10 tetrahydro-1H-benzazepine as a white solid (0.37 g).

The above product (0.30 g) was heated in 3N HCl (50 ml) to reflux overnight. The resulting solution was evaporated to dryness and triturated with acetone to give a white solid.  
15 This was recrystallised from n-propanol/ HCl to give the title compound as white crystals (0.21 g), m.p. 277-281°C.

#### Example 6

##### 20 7-Methoxy-6-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride

The title compound was prepared following the procedures described in Example 2, by heating 3-acetyl-7-  
25 methoxy-6-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride (0.15g) in 3N.HCl (9mL) at reflux. The product, 7-methoxy-6-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride, was isolated as described, and recrystallised from n-propanol to give small yellow crystals (0.077g), m.p.  
30 258-61°C decomp.

#### Example 7

##### 35 6-Bromo-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride

The title compound was prepared following the procedures described in Example 2, by heating 3-acetyl-6-bromo-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine (0.20g) in  
40 3N.HCl (11 mL) at reflux. The product, 6-bromo-7-methoxy-

2,3,4,5-tetrahydro-1H-benzazepine hydrochloride, was isolated as described and recrystallised from n-propanol to give white needles (0.12g), m.p. 255-60°C.

5

**Example 8****8-Acetyl-7-hydroxy-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride**

10 Tin tetrachloride (2.4 mL) was added dropwise, with stirring to a solution of acetyl chloride (1.46 mL) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL), at room temperature. Stirring was continued for a further 1 hour, and then a solution of 7-methoxy-3-acetyl-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride (3.0g) in  
15 CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added over a period of 20 minutes. The mixture was left to stir for 16 hours, and then partitioned between 3N.HCl and CH<sub>2</sub>Cl<sub>2</sub>. The aqueous layer was re-extracted and the combined organic layers were washed with saturated sodium bicarbonate solution and then H<sub>2</sub>O, dried  
20 (MgSO<sub>4</sub>) and evaporated. The residue was dissolved in methanol and treated with charcoal. The filtrate was evaporated to dryness and the residue extracted twice with boiling benzene, the extracts decanted combined and evaporated to give a solid which was triturated with ether.  
25 The product, 3,8-diacetyl-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine, was obtained as an off-white solid (1.7g), m.p. 142-6°C.

30 The 3,8-diacetyl-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine (0.20g) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and cooled to ca -70°C (acetone/solid CO<sub>2</sub> bath). Boron trichloride (1.0M solution in CH<sub>2</sub>Cl<sub>2</sub>; 1.53 mL) was added from a syringe over 10 minutes. The mixture was allowed to warm slowly to room temperature (1 hour) and then stirred for a further 30  
35 minutes. The reaction was quenched by the addition of H<sub>2</sub>O and the mixture was partitioned between water and CH<sub>2</sub>Cl<sub>2</sub>. The aqueous layer was re-extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic layers washed with water and brine, and dried (MgSO<sub>4</sub>). Evaporation gave a gum which was purified by  
40 flash chromatography (SiO<sub>2</sub>; CHCl<sub>3</sub>/MeOH). The product, 3,8-

diacetyl-7-hydroxy-2,3,4,5-tetrahydro-1H-benzazepine, crystallised from ether as an off-white solid (0.129g), m.p. 131-4°C.

- 5       The above diacetyl compound (0.121g) was heated at reflux in 3M.HCl (3.7 mL) for 16 hours. The solution was then evaporated to dryness, giving a yellow-orange crystalline solid. This was recrystallised from n-propanol containing dissolved HCl gas, to yield the product, 8-acetyl-  
10   7-hydroxy-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride, as small orange crystals (0.064g), m.p. 241-7°C decomp.

#### Example 9

- 15   **7-Hydroxy-8-methylsulphinyl-2,3,4,5-tetrahydro-1H-benzazepine**

- Aluminium chloride (1.71 g) was added to dichloromethane (50 ml) at room temperature, and a solution  
20   of 3-acetyl-7-methoxy-8-methylsulphinyl-2,3,4,5-tetrahydro-1H-benzazepine (0.90 g) in dichloromethane was added dropwise with stirring over 3h. After leaving the mixture to stir overnight at room temperature, the dichloromethane solution was decanted from the precipitated gum. The latter was  
25   digested with 1M sodium hydroxide solution, and the resulting aqueous solution was washed with dichloromethane, acidified to pH<sub>2</sub> with conc. HCl and extracted (3x) with chloroform. The extract was dried (MgSO<sub>4</sub>), evaporated to an oil, and purified by chromatography (SiO<sub>2</sub>; MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give 3-  
30   acetyl-7-hydroxy-8-methylsulphinyl-2,3,4,5-tetrahydro-1H-benzazepine (0.72 g).

- The above product (0.64 g) was heated with 1M sodium hydroxide solution (10 ml) at 100°C overnight. After  
35   cooling, the mixture was passed down an ion exchange column (Amberlite CG50; NH<sub>4</sub><sup>+</sup>) and eluted with water. The resulting eluate was evaporated to dryness, extracted with hot methanol, treated with activated charcoal, filtered and

evaporated to a green gum. This crystallized on addition of acetonitrile to give the title compound (0.45 g), mp 175-8°C.

#### Example 10

5

#### 7-Hydroxy-8-trifluoromethylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine

3-Acetyl-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine  
10 (7.0 g) was dissolved in dry dichloromethane (100 ml), cooled in an ice bath, and treated dropwise with chlorosulphonic acid (13.9 g), with stirring. The mixture was stirred for a further 2 1/2 h at room temperature and then poured carefully onto ice. The resulting brown oil was partitioned between  
15 dichloromethane and water, and the aqueous layer was extracted further with dichloromethane. Combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated to give 3-acetyl-7-methoxy-8-chlorosulphonyl-2,3,4,5-tetrahydro-1H-benzazepine (4.5 g).

20

The above product (3.95 g) was dissolved in acetic acid (75 ml), and stannous chloride dihydrate (11.2 g) and conc. HCl (15 ml) were added. The mixture was stirred at 75°C for 1 h then poured into ice water and shaken with ethyl acetate.  
25 The solid thus produced was combined with the ethyl acetate extracts and evaporated to dryness in vacuo. This crude product was shaken with dry ethanol (200 ml) and filtered. The resulting solid was stirred with 1M NaOH solution (100 ml) for 30 min., filtered, acidified with conc. HCl and  
30 extracted with chloroform. The extracts were combined, dried (MgSO<sub>4</sub>) and evaporated to dryness to give 3-acetyl-7-methoxy-8-mercapto-2,3,4,5-tetrahydro-1H-benzazepine (1.86 g).

This product (1.22 g) was dissolved in dry DMF (50 ml)  
35 and potassium carbonate (1.33 g) added. Trifluoromethyl iodide was bubbled through the solution, while irradiating with U.V. light, with cooling, for 5 h. Most of the DMF was removed under vacuum, and the residue was partitioned between

- chloroform and 1M NaOH solution. The organic phase was dried (MgSO<sub>4</sub>) and evaporated to dryness. The residue was purified by chromatography (SiO<sub>2</sub>; CHCl<sub>3</sub>/MeOH) to give 3-acetyl-7-methoxy-8-trifluoromethyl-2,3,4,5-tetrahydro-1H-benzazepine (0.33 g).

- The above product (1.0 g) was dissolved in 1,2-dichloro-ethane (75 ml) and meta-chloro perbenzoic acid (2.26 g) was added. The mixture was heated under reflux for 2 h.
- The resulting cooled solution was washed with 1M NaOH solution, dried (MgSO<sub>4</sub>) and evaporated to dryness leaving 3-acetyl-7-methoxy-8-trifluoromethylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine (0.95 g).

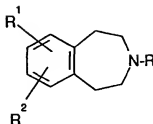
- This product (0.50 g) was dissolved in dichloromethane (100 ml) and boron tribromide (0.71 g) was added dropwise with stirring at room temperature overnight. Methanol was added cautiously, dropwise, and the solvents were removed in vacuo. The residual green oil consisting of the 7-hydroxy compound was dissolved in chloroform and washed with 1M NaOH solution.

- The aqueous phase was separated and heated at 100°C for 40 h, cooled, and passed down an ion exchange column (Amberlite CG-50(H)). The relevant fractions were combined and evaporated to dryness to leave a residue which was chromatographed (SiO<sub>2</sub>; CHCl<sub>3</sub>/MeOH/MH<sub>4</sub>OH) to give a product which was crystallized under acetonitrile to give the title compound (0.12 g), mp >273°C.



## CLAIMS:

1. The use of a compound of structure (I)



Structure (I)

in which:

- R is hydrogen, C<sub>1-6</sub>alkyl or C<sub>3-5</sub>alkenyl;  
 10 R¹ is NO<sub>2</sub>, cyano, halo, COR<sup>3</sup>, SO<sub>n</sub>R<sup>4</sup> or SO<sub>n</sub>NR<sup>5</sup>R<sup>6</sup>;  
 R² is hydrogen, hydroxy or C<sub>1-4</sub>alkoxy;  
 R³ is hydrogen, C<sub>1-4</sub>alkyl, OR<sup>5</sup> or NR<sup>5</sup>R<sup>6</sup>;  
 R⁴ is C<sub>1-6</sub>alkyl or halo C<sub>1-6</sub>alkyl;  
 15 R⁵ and R⁶ are hydrogen or C<sub>1-6</sub>alkyl or C<sub>3-6</sub> cycloalkyl; and  
 n is 1 or 2;  
 or a pharmaceutically acceptable salt thereof in the  
 manufacture of a medicament for the treatment of portal  
 hypertension and/or migraine.

20

2. The use of a compound according to claim 1 in which  
 R¹ is at the 8-position and R² is at the 7-position of the  
 ring of the compound of structure (I).

25

3. The use of a compound according to claim 1 or claim  
 2 in which R¹ is SO<sub>2</sub>R<sup>3</sup>, R² is hydrogen, alkoxy or hydroxy and  
 R is hydrogen.

4. The use of a compound according to any of claims 1  
 30 to 3 in which R³ is methyl and R² is hydroxy.

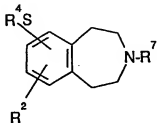
5. The use of a compound according to claim 1 which is 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine.

6. A compound according to claim 1 which is:
- 7-methoxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine;
  - 7-methoxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine;
  - 7-hydroxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine;
  - 7-methoxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine;
  - 7-bromo-8-hydroxy-2,3,4,5-tetrahydro-1H-benzazepine;
  - 7-methoxy-6-nitro-2,3,4,5-tetrahydro-1H-benzazepine;
  - 6-bromo-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine;
  - 8-acetyl-7-hydroxy-2,3,4,5-tetrahydro-1H-benzazepine;
  - 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine; and
  - 7-hydroxy-8-trifluoromethylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine;
- or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a compound according to claim 6 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or excipient therefor.

8. A process for preparing a compound of Structure (I) wherein R, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and n are as defined in claim 1 and R<sup>1</sup> represents SO<sub>n</sub>R<sup>4</sup>, -COR<sup>3</sup>, NO<sub>2</sub> or halogen, which comprises :

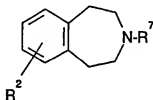
- a) to prepare a compound of structure (I) where R<sup>1</sup> represents -SO<sub>n</sub>R<sup>4</sup>, the reaction of a compound of structure (II) :



## Structure (II)

(wherein  $R^2$  and  $R^4$  are as hereinbefore defined and  $R^7$  is an N-protecting group) with an oxidising agent, in the presence  
5 of titanium trichloride;

b) to prepare a compound of structure (I) wherein  $R^1$  represents  $-COR^3$ ,  $NO_2$  or halogen, the reaction of a compound  
10 of structure (III) :



Structure (III)

wherein  $R^2$ ,  $R^3$  and  $R^7$  are as hereinbefore defined) with an  
15 appropriate acylating, nitrating or halogenating agent  
respectively; followed in each case by removal of the N-  
protecting group, and if desired salt formation.

9. Use of a 5-HT<sub>2</sub> receptor agonist in the treatment of  
20 portal hypertension.

10. Use of a 5-HT<sub>1</sub>-like-receptor agonist in the  
treatment of portal hypertension.

25 11. Use of a compound which is an agonist at both 5-HT<sub>2</sub>  
and 5-HT<sub>1</sub>-like-receptors in the treatment of portal  
hypertension.

12. Use of a 5-HT<sub>2</sub> receptor agonist in the treatment  
30 and prophylaxis of migraine.

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**